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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
CANELLA, K	
ART UNIT	PAPER NUMBER
1642	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/501,179	Wang et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-26* is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-26* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *3,4,7*

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

1. Claims 1-26 are pending and examined on the merits.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 6, 19 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A)Claim 6 recites "biological marker clusters". As there is no definition or mention of "biological marker clusters" in the specification, but figure 1H illustrates cellular clusters, it is not clear what clusters are encompassed by claim 6.

(B)Claims 19 and 20 recite "metastatic cancer". As metastasis is defined as the transfer of disease to distant organs not directly connected to the site of the original disease, it is not clear if the claim is encompassing the detection of circulating malignant cells, or the detection of secondary tumors resulting from the seeding and growth of said circulating malignant cells in distant organs. For purpose of examination metastatic cancer cells will be read as circulating malignant cells.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 1-18 are drawn to a method of classifying cancer cells in a body fluid comprising the isolation of circulating cancer cells and the classification of said cells as terminal, proliferative and/or intermediate. Claims 19 and 20 are drawn to a method of determining the presence or absence of metastatic cells by the isolation of circulating cancer cells and the classification of said cells as terminal, proliferative and/or intermediate and assessing whether metastatic cancer is present based on said classification. Claims 21-26 are drawn to a method of determining the efficacy of a medical procedure comprising conducting a first and a second isolation of circulating cancer cells and the classification of said cells as terminal, proliferative and/or intermediate, wherein the second isolation is conducted after the administration of the medical procedure, whereby the efficiency of the medical procedure is assessed based on the classification of the cancer cells as determined in the second isolation relative to the classification of the cancer cells as determined in the first isolation. The specification teaches the isolation of circulating prostate and breast cells, and describe a classification method wherein the isolated cells are classified on the basis of size and ploidy, into intermediate/indeterminate, proliferative or terminal cancer cells. The specification outlines a "proliferative" pathway and a "terminal" pathway arising from intermediate cell B in Figure 1. The specification teaches that cells of the terminal pathway may die or be destroyed, but cells of the proliferative pathway may eventually become terminal cells. The specification does not teach the relative partitioning of the intermediate cell as exmplified in Figure 1B into the terminal vs proliferative pathway. Furthermore, the disclosure lacks a link between the resulting classifications of said isolated tumor cells in terms of absolute numbers and percentages, and the diagnosis of metastatic cancer. Therefore, it is not evident from the specification how to use the proposed classification presented in the instant specification. Table 1 on page 43 illustrates the percentage of isolated circulating

cancer cells classified into each type A through F. However, the specification does not correlate the percentage of cells classification in any category, A through F, with the diagnosis of metastatic disease, and it cannot be presumed that proliferation pathway is one and the same with metastatic disease. The specification provides no teachings regarding the efficacy of therapy on said individual having a number of circulating cancer cells classified as intermediate/indeterminate, in light of the teaching in the specification regarding the potential of the intermediate cell to enter either the proliferative or terminal pathway. The specification teaches that 70-75% of circulating breast cancer cells are classified as intermediate, 5-10.1% are classified as proliferative cells and 10.1-21% are classified as terminal cells. The specification does not correlate the percentages or absolute numbers of cells classified as proliferative and/or intermediate with the likelihood of metastatic breast cancer or metastatic prostate cancer. The specification does not correlate the change in percentages or absolute numbers of cells classified as proliferative and/or intermediate with the efficacy of treatment. Further, the specification teaches that proliferative cells may not progress beyond 1G or 1H, or may become terminal cells 1C, 1D, 1E or 1F. Given these complexities of the competing pathways, the specification does not correlate the percentages and absolute numbers of cells in each category with metastatic disease or efficacy of treatment. In addition, claim 21 can encompass a first and second isolation and characterization of circulating cancer cells, carried out before the administration of a medical treatment and it is not clear how such a protocol would be used to determine the efficacy of a treatment which was administered after the second isolation. Furthermore, if applicant was able to overcome the rejection under 35 U.S.C. 112, first paragraph, the specification is not enabling with respect to cancers other than prostate or breast, identification of the intermediate cell "B", or identification of a "terminal" pathway.

(A)As drawn to a terminal pathway

The specification teaches that the intermediate cell "B" can give rise to a proliferative pathway characterized by proliferating cell antigens and symmetric mitosis, or cell "C"

characterized by polyploidy and the ability to produce a nucleate and an anucleate cell "D" and ", respectively. The specification teaches that broken cells "F" arise from cells "D" and/or "E" and that both cells "D" and "E" are positive for apoptotic markers and are therefore terminal. However, the specification does not provide objective evidence that the presence of apoptotic markers on cell "D" or "E" results in the apoptosis of said cells, and teaches against what is known in the art, that cells undergoing apoptosis in vivo do not result in the accumulation of broken cells but are removed prior to breaking up by phagocytes (Leverrier et al, Current Biology, 2001, Vol. 11, pp. 195-199). Therefore, the presence of broken cells "F" cannot be indicative of apoptosis of cell "D" or "E", but can be indicative of the rupture of large, fragile cell "C" during isolation. As cell "D" is not anucleate and has not been demonstrated to undergo apoptosis, it can potentially continue to propagate, thus, there is no objective evidence for the designation of a "terminal" pathway. Given this lack of guidance in the specification regarding the fate of cell "D", one of skill in the art would not known how to use the claimed method of classification of circulating cancer cells.

(B)As drawn to the identification of cell types "A", "B" and "C".

Claim 3 is drawn to a method of classifying a fragile, large terminal cancer cell of about 10-50 micrometers in diameter from bodily fluid. The specification teaches on pg. 12, line 10, a fragile large cancer cell of about 20 to about 50 micrometers, and more specifically, about 30 to about 50 micrometers. One of skill in the art would be subject to undue experimentation in order to classify a cancer cell from bodily fluid having a diameter of 10 micrometers, as it is not associated with the large fragile cancer cell of type "C" as described in the specification. Claims 9 and 10 are drawn to a method of classifying a proliferative cancer cell of about 10-20 micrometers in diameter from bodily fluid. The specification teaches that the stem cell "A" is about 10-20 micrometers in diameter. The specification teaches that stem cell "A" gives rise to intermediate cell "B", which can then either follow the proliferative or the terminal pathway. The specification does not teach that stem cell "A" is committed to the proliferative pathway (pg. 11, lines 12-14).

Further, the specification teaches that most of the stem-cells "A" are found in resting phase or interphase which is not indicative of rapid, proliferating cells. Thus, one of skill in the art would not be able to classify a cell having a diameter of 10-20 micrometers as a proliferative cell. Furthermore, it would be difficult to discern between cell types "A" and "B" given the guidance in the specification. The specification teaches cell "B" as having a diameter of about 20-30 micrometers and "more cytoplasm" than cell "A" (pg. 12, lines 5-7). The specification teaches cell "A" as having a 10-20 micrometer diameter and "less structural network" than cell "B" (pg. 10, line 30). Given these rudimentary guidelines, one of skill in the art would be subject to undue experimentation in order to determine if a circulating cancer cell of diameter of about 20 microns was classified as type "A" or "B" as relying on descriptors of "more cytoplasm" or "less structural network" without descriptions of each cell type that did not rely on differences between the two cell types. It is conceivable that one of skill in the art, when practicing the claimed method, would not have the opportunity to observe both cell types in any given sample, therefore the potential classification of a circulating cancer cell of intermediate size would be impossible as the definition relies on small differences between parameters, not absolute values of parameters associated with cell type "A" and "B".

(C)As drawn to the classification of circulating cancer cells not arising from the prostate or the breast.

Claims 1-18 are drawn to a method of classifying cancer cells in a body fluid comprising the isolation of circulating cancer cells and the classification of said cells as terminal, proliferative and/or intermediate. Claims 19 and 20 are drawn to a method of determining the presence or absence of metastatic cells by the isolation of circulating cancer cells and the classification of said cells as terminal, proliferative and/or intermediate and assessing whether metastatic cancer is present based on said classification. Claims 21-26 are drawn to a method of determining the efficacy of a medical procedure comprising conducting a first and a second isolation of circulating cancer cells and the classification of said cells as terminal, proliferative and/or intermediate,

wherein the second isolation is conducted after the administration of the medical procedure, whereby the efficiency of the medical procedure is assessed based on the classification of the cancer cells as determined in the second isolation relative to the classification of the cancer cells as determined in the first isolation. The specification teaches the isolation of circulating prostate and breast cells, and describe a classification method wherein the isolated cells are classified on the basis of size and ploidy, into intermediate/indeterminate, proliferative or terminal cancer cells. The specification teaches specific methods for the isolation of circulating breast or prostate cells from 10-20 ml of peripheral blood and the morphological analysis and classification of said cells based on the further characterization by antibodies. For example, the specification teaches cytokeratin staining of proliferative and terminal prostate and breast cells. However, it is known in the art that some cancer cells are not positive for cytokeratin. For example, lung adenocarcinoma was differentiated from pleural epithelial mesothelioma on the basis of negative cytokeratin immunostaining in the case of the adenocarcinoma cells (Ordonez, American journal of surgical Pathology, 1998, vol. 22, pp. 1215-1221). Further, the specification teaches specific cell diameters as an integral part of the classification of cell types, and there is no objective evidence that other cancers, for example sarcomas and lymphomas, would fall in the same range of diameters as put forth in the specification for prostate and breast cancer cells. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the invention on other types of cancer cells beyond breast and prostate as one of skill in the art would be forced to investigate the cellular parameters that could be used to identify cell types A-I which are indicative of other types of circulating cancer cells, and further, there is no objective evidence to indicate that a "terminal" pathway would exist in such circulating cancer cells.

Conclusion

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

GEETHA P. BANSAL
PRIMARY EXAMINER

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
April 22, 2001